Amend the paragraph bridging pages 1 and 2 to read as follows:

--Two mechanisms of cell death in the body are recognized, necrosis and apoptosis. Apoptosis is the process of programmed cell death, described by Kerr et al in 1992, (Kerr JFR, Wyllie AH, Currie AR (1992). "Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *"British Journal of Cancer* **26:** 239-257") by which steady-state levels of the various organ systems and tissues in the body are maintained as continuous cell division and differentiation takes place. Cells undergoing apoptosis often exhibit distinctive morphological changes such as a pronounced decrease in cell volume, modification of the cytoskeletons resulting in pronounced membrane blebbing, a condensation of the chromatin, and degradation of the DNA into oligonucleosomal fragments. Following these morphological changes, an apoptotic cell may break up into a number of small fragments known as apoptotic bodies, comprising membrane-bound bodies containing intact organelles, chromatin, etc. Apoptotic bodies are normally rapidly removed from the body by phagocytosis by macrophages, dendritic cells and other antigen-presenting cells, before they can become lysed and release their potentially pro-inflammatory intracellular contents.--

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Amend the paragraph at page 3, lines 3-16, to read as follows:

--Many cells undergoing apoptosis can be identified by a characteristic 'laddering' of DNA seen on agarose gel electrophoresis, resulting from cleavage of DNA into a series of fragments. These changes occur a few hours before death of the cell as defined by the ability of a cell to exclude vital dyes. The appearance of DNA laddering on agarose gel electrophoresis following extraction of DNA from cells is one recognized method of identification of apoptosis in cells (Loo, D.T. and Rillema, J.R. (1998) "Measurement of Cell Death," *Methods in Cell Biology* **57**: 251-264), although it is not always sensitive enough to detect apoptosis. *In situ* labeling of nuclear DNA fragmentation, for example, using commercially available terminal dUTP nick end labeling (TUNEL) assays, is an alternative and more reproducible measure for the determination of fragmented DNA in

B2

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apoptotic cells and cells undergoing apoptosis (Gavrieli Y, Sherman Y, Ben-Sasson SA (1992) "Identification of programmed cell death in situ via specific labelling of nuclear DNA fragmentation," *Journal of Cell Biology* **119:** 493-501).--

Amend the paragraph at page 3, lines 17-26, to read as follows:

--During apoptosis, phosphatidylserine becomes exposed externally on the cell membrane (Fadok VA, Voelker DR, Campbell PA, Cohen JJ, Bratton DL, Henson PM (1992), "Exposure of phosphatidylserine on the surface of apoptotic lymphocytes triggers specific recognition and removal by macrophages". *Journal of Immunology* **148:** 2207-2216) and this exposed phosphatidylserine binds to specific receptors to mediate the uptake

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and clearance of apoptotic cells in mammals (Fadok VA, Bratton DL, Rose DM, Pearson A, Ezekewitz RAB, Henson PM (2000), "A receptor for phosphatidylserine-specific clearance of apoptotic cells", *Nature* **405:** 85-90). The surface expression of phosphatidylserine on cells is another recognized method of identification of apoptotic cells.--

Amend the paragraph at page 4, lines 1-9, to read as follows:

--Changes in mitochondrial integrity are intimately associated with apoptosis, resulting in alterations in mitochondrial membrane permeability and the release of cytochrome-c from the mitochondria into the cell cytoplasm (Susin, S.A., Lorenzo, H.K., Zamzami, N., Marzo, I, Brenner, C., Larochette, N., Prevost, M.C., Alzari, P.M. and Kroemer, G.

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(1999) "Mitochondrial Release of Caspase-2 and -9 during the Apoptotic Process", *Journal of Experimental Medicine,* **189**: 381 - 394). Measurement of changes in mitochondrial membrane potential, reflecting changes in mitochondrial membrane permeability, is another recognized method of identification of apoptotic cells.--

Amend the paragraph at page 6, lines 3-10, to read as follows:

--Normally, the endothelium maintains vascular homeostasis by responding to physiological stimuli, for example, changes in blood flow, oxygen tension etc., by adaptive alteration of function. Dysfunctional endothelium has an impaired response to such physiological stimuli, and can ultimately lead to medical disorders. A number of subsets of endothelial dysfunction have been recognized, including Endothelial Activation, and Endothelial-mediated Vasodilatory Dysfunction (see De Caterina (2000). "Endothelial dysfunctions: common denominators in vascular disease". Current Opinions in Lipidology 11:9-23).--

Amend the paragraph bridging pages 6 and 7 to read as follows:

--Endothelial-mediated Vasodilatory Dysfunction is characterized by a reduction or loss of endothelium-dependent vasodilation and involves "decreased nitric oxide bioavailability" (decreased production, increased destruction and/or decreased sensitivity to nitric oxide). (De Caterina (2000), cited above). Nitric oxide induces vasodilation by relaxing the smooth muscle cells of the blood vessel wall. Endothelial-mediated Vasodilatory Dysfunction can be measured as a reduction in vasodilation in response to acetylcholine, or as a reduced vasodilatory response following occlusion of arterial blood flow (reactive hyperaemia) for example using a sphygmomanometer cuff. As well as leading to a reduction in vasodilation, decreased endothelial nitric oxide bioavailability can also result in an increase in the production of vaso-constriction and hypertension. Platelet aggregation is inhibited by nitric oxide, hence a decrease in nitric oxide bioavailability can lead to an increase in platelet aggregation and consequent thrombosis. These are just a few examples of how decreased nitric oxide bioavailability resulting from Endothelial-mediated Vasodilatory Dysfunction can have pathological consequences.--

Amend the paragraph bridging pages 7 and 8 to read as follows:

--"Apoptotic cells" and "apoptotic bodies," as the terms are used herein, means cells and cell bodies which exhibit one or more of the following apoptosis-characterizing features: surface exposure of phosphatidylserine, as detected by standard, accepted methods of detection such as Annexin V staining; alterations in mitochondrial membrane permeability measured by standard, accepted methods (e.g. Salvioli, S., Ardizzoni, A., Franceschi, C. Cossarizza, A. (1997) "JC-1, but not DiOC6(3) or Rhodamine 123, is a Reliable Fluorescent Probe to assess Delta Psi Changes in Intact Cells: Implications for Studies on Mitochondrial Functionality during Apoptosis," *FEBS Letters* **411:** 77-82); evidence of DNA fragmentation such as the appearance of DNA laddering on agarose gel electrophoresis following extraction of DNA from the cells (Teiger, E., Dam, T.V., Richard, L., Wisnewsky, C., Tea, B.S., Gaboury, L., Tremblay, J., Schwartz, K. and Hamet, P. (1996) "Apoptosis in Pressure Overload-induced Heart Hypertrophy in the Rat," *Journal of Clinical Investigation* **97**; 2891-2897), or by *in situ* labeling (see Gavrieli et al., 1992, referenced above).--

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Amend the paragraph at page 9, lines 5-10, to read as follows:

--A variety of methods of inducing apoptosis in mammalian cells, so as to create apoptotic cells and/or apoptotic bodies, are known in the art and essentially any of these can be adopted in preparing apoptotic bodies for use in the present invention. One such method is the subjection of the cells to ionizing radiation (γ-rays, x-rays, etc.) and/or non-ionizing electromagnetic radiation including ultraviolet light. Apoptosis can be induced by subjecting cells to ultrasound.--

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Amend the paragraph bridging pages 9 and 10 to read as follows:

--Another method is the treatment of the cells with drugs such as non-specific protein kinase inhibitors as exemplified by staurosporine (see Bombeli, Karsan, Tait and Hirlan, (1997) "Apoptotic Vascular Endothelial Cells Become Procoagulant", Blood, Vol. 89:2429-2442). Also, certain chemotherapeutic agents used for the treatment of malignant tumours induce apoptosis, for example, adriamycin, as can statin drugs (3-hydroxy-3methylglutaryl coenzyme A reductase inhibitors) (Guijarro C, Blanco-Colio LM, Ortego M, Alonso C, Ortiz A, Plaza JJ, Diaz C, Hernandez G, Edigo J (1998), "3-hydroxy-3methylglutaryl coenzyme A reductase and isoprenylation inhibitors induce apoptosis of vascular smooth muscle in culture," *Circulation Research* **83:** 490-500) and colcicine (Suzuki Y (1998)", "Cell death, phagocytosis and neurogenesis in mouse olfactory epithelium and vomeronasal organ after colcicine treatment," *Annals of the New York Academy of Sciences* **855:** 252-254). The use of ligands for death receptors on cells, such as Fas-ligand, will be apparent for inducing apoptosis from the discussion of apoptosis above. A further method is the application of oxidative stress to cells extracorporeally (see for example Buttke and Sandstrom (1994) "Oxidative Stress as a Mediator of Apoptosis," Immunology Today, Vol. 15:7-10). This can be achieved by treating the cells, in suspension, with chemical oxidizing agents such as hydrogen peroxide, other peroxides and hydroperoxides, ozone, permanganates, periodates, and the like. Biologically acceptable oxidizing agents are preferably used, so as to reduce potential problems associated with residues and contaminations of the apoptotic cells and/or apoptotic bodies so formed.--

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Amend the paragraph at page 10, lines 16-27, to read as follows:

--In preparing the apoptotic cells and/or apoptotic bodies, care should be taken not to apply excessive levels of oxidative stress, radiation, drug treatment, etc., since otherwise there is a significant risk of causing necrosis of at least some of the cells under treatment.

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